I. Pending Claims and Amendments

Claims 43-47, 54-60, 62 and 65-68 were currently pending. Claims 43-47, 54-60, 62 and 65-68 are amended so that they are drawn to an oligonucleotide rather than a pharmaceutical composition. Claim 69, drawn to "compositions comprising an oligonucleotide according to any of claims 43-47, 54-60, 62 and 65-68" is added in this amendment. Claim 70, drawn to "pharmaceutical compositions comprising an oligonucleotide according to any of claims 43-47, 54-60, 62 and 65-68 and a pharmaceutically acceptable carrier" is added in this amendment. No new matter has been added.

II. Sequence Listing

Applicants are submitting a Sequence Listing under separate cover.

III. Rejections under 35 U.S.C. §102(b)

Claims 43-47, 57-58 and 62 were rejected by the Examiner as anticipated by Kurreck et al. (*Nucleic Acid Research* 40:1911, 2002; "Kurreck"). The Examiner argued that Kurreck teaches LNA-DNA-LNA mixmers, gapmers and end blocks. More specifically, the Examiner argues that Kurreck teaches an 18 nucleotide LNA-DNA-LNA oligonucleotide having two regions of "1 to 5 oxy LNA monomers in the beta configuration flanking a third, or central region.... consisting of DNA and optionally 1 or 2 LNAs."

Applicants respectfully traverse this rejection. Claim 43 is drawn to an oligionucleotide having the overall formula A-B-C in which "A consists of between 2 and 10 nucleotide units, wherein between 1 and 5 of the nucleotide units in A are locked nucleotide units; B consists of between 1 and 10 nucleotide units, wherein B comprises <u>at least one alpha-L-oxy LNA nucleotide unit</u>; and C consists of between 2 and 10 nucleotides units wherein between 1 and 5 of the nucleotide units in C are locked nucleotide units" (emphasis added). The remaining claims depend directly or indirectly from claim 43. Thus, all of the claims require the presence of at least one **alpha-L**-oxy LNA nucleotide.

Differences Between Alpha-L-oxy LNA and Beta-D-oxy LNA

As the specification of the present application explains, alpha-L-oxy LNA (sometimes called alpha-L-LNA) differ from LNA, which are sometimes referred to as beta-D-oxy LNA or beta-D-LNA. For example, see paragraph 0061 of the present application, which provides a general formula for alpha-L-LNA derivatives and beta-D-LNA derivatives. The structures alpha-L-oxy LNA and beta-D-oxy LNA are depicted below in Figure 1.

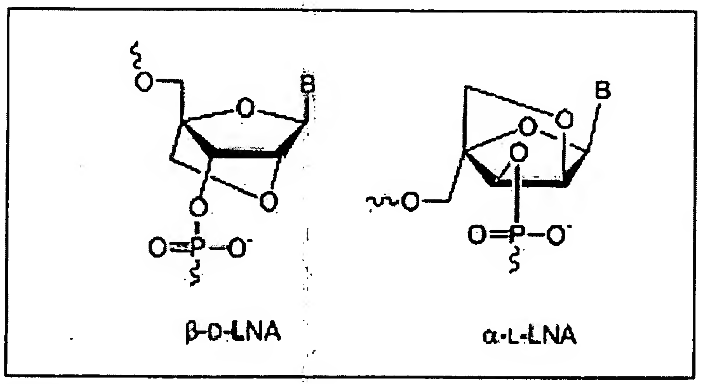

FIGURE 1

As can be seen from the illustration above, alpha-L-oxy LNA and beta-D-oxy LNA are diasteroemers and have very different structures. As the specification explains (see paragraph 0005), the two molecules have very different properties. To understand the different properties of alpha-L-oxy-LNA and beta-D-oxy-LNA it is important to first understand that the furanose ring of deoxyribose at room temperature exists in an equilibrium between the C2'-endo (S-type) conformation and the C3'-exo (N-type) conformation. These two conformations are depicted below in Figure 2.

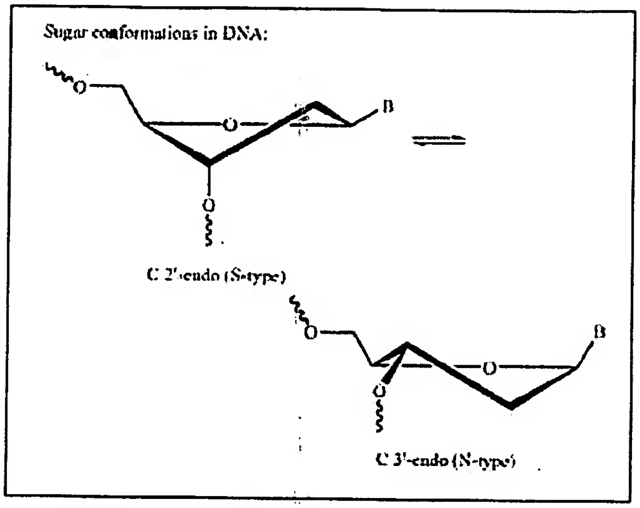

FIGURE 2

The furanose ring of both deoxyribonucleotides and ribonucleotides is flexible, shifting between the C2'-endo (S-type) configuration and the C3'-endo (N-type) configuration. In deoxyribonucleotides the furanose ring exists primarily in the C2'-endo (S-type) configuration. In contrast the furanose ring of ribonucleotides exists primarily in the C3'-endo (S-type) configuration.

The furanose ring of **beta-D**-oxy-LNA (LNA) is locked in the **C3'-endo** (N-type) configuration, the dominant configuration in **RNA**. In contrast, the furanose ring of **alpha-L-**oxy LNA is locked in the **C3'-exo** (N-type) configuration, dominant configuration in **DNA**. Thus, alpha-D-oxy LNA and beta-D-oxy-LNA (LNA) are different types of nucleotides.

<u>Kurrek Does Not Describe Oligonucleotides Containing Alpha-L-oxy LNA</u>

Kurrek describes oligos that include "LNA". This is the common shorthand name for beta-D-oxy LNA, a nucleotide that differs from alpha-L-oxy LNA. Because Kurreck does not describe an oligonucleotide that include alpha-L-oxy LNA, and instead describes oligonucleotide that include beta-D-oxy LNA, Kurrek cannot anticipate that present claims. As the Examiner pointed out, Kurreck obtained the LNA from Prologia. As further evidence for the fact that Kurreck does not disclose alpha-L-oxy LNA, Applicant encloses an August 8, 2008 letter to

Troels Koch, a co-inventor of the present application from Andreas Wolter, the Managing Director of Sigma-Aldreich Biochemie GmbH (**Exhibit A**). In the letter Dr. Wolter confirms that Sigma-Aldrich Biochemic GmbH and all of its precursor companies, including Proligo LLC and Proligo GmbH "have never offered sold or marketed any α-L-LNA nucleosides of any kind." In the letter, Dr. Wolter confirms that "β-D-LNA were sold to the public until the end of 2007."

In view of forgoing, it is clear that the LNA used by Kurreck were beta-D-oxy LNA and not the alpha-L-oxy LNA required by the present claims.

Applicant respectfully requests that the rejection of claims 43-47, 57-58 and 62 under 35 U.S.C. §102(b) be reconsidered and withdrawn.

IV. Rejections under 35 U.S.C. §103

The Examiner rejected claims 43-47, 54-60, 62 and 65-68 as obvious in view of Kurreck taken with Monia et al. (U.S. Patent 6,884,787) Crinella et al. (Nucleic Acids Research (30:243, 2002) and Wengel et al. (WO 99/14226). The examiner stated that Kurreck was relied on for the teachings described in the 35 U.S.C. §102(b) rejection and went on to state that even if the oligonucleotides of Kurreck were not present in a composition that included a pharmaceutically acceptable carrier, the other references made it obvious to combine the oligionucleotides of Kurreck et al. with a pharmaceutically acceptable carrier.

As discussed above, Kurreck does not disclose oligonucleotides that include an alpha-L-oxy LNA as required by the present claims. Likewise none of Monia et al. (U.S. Patent 6,884,787) Crinella et al. (*Nucleic Acids Research* 30:243, 2002) and Wengel et al. (WO 99/14226) disclose an oligonucleotide that include an alpha-L-oxy LNA as required by the present claims. Thus, the cited references, no matter how combined, cannot be seen as suggesting any of the claimed oligonucleotides or pharmaceutical compositions.

Applicant respectfully requests that the rejection of claims 43-47, 57-58 and 62 under 35 U.S.C. §103 be reconsidered and withdrawn.

V. Rejections under 35 U.S.C. §112, first paragraph (enablement)

Claims 43-47, 54-60, 62 and 65-68 were rejected under 35 U.S.C. §112, first paragraph as not enabled.

Citing Jen et al. (*Stem Cells* 18:307-319, 2000), the Examiner argued that the use of antisense oligonucleotides in therapy is unpredictable, and therefore, claims drawn to pharmaceutical compositions are not enabled. The Examiner stated that removing the term "pharmaceutical" from the claims would overcome this rejection.

<u>Claims 43-47, 54-60, 62 and 65-69</u>

Claims 43-47, 54-60, 62 and 65-68 have been amend to recite an oligonucleotide rather than a pharmaceutical composition comprising an oligonucleotide. New claim 69 is drawn to a composition comprising an oligonucleotide according to any of claims 43-47, 54-60, 62 and 65-68. In as much as the Examiner stated that removing the term "pharmaceutical" from the claims would overcome the enablement rejection. Applicant respectfully requests that the enablement rejection of claims 43-47, 54-60, 62 and 65-68 be withdrawn and that the rejection not be applied to claim 69.

<u>Claim 70</u>

Claim 70 is drawn to "a pharmaceutical composition comprising an oligonucleotide according to any of claims 43-47, 54-60, 62 and 65-68 and a pharmaceutically acceptable carrier".

The Examiner argued that it would require undue experimentation to use the claimed pharmaceutical compositions because the use of such compositions in unpredictable. The Examiner stated that given this unpredictability, one would "require specific guidance to ... use the claimed pharmaceutical compositions to treat one ore more disorders *in vivo* in any given patient." The Examiner also stated that the present application does not illustrate "the proposed use of the compositions to treat any organism, mammal, or human subject." The Examiner

stated that problems related to the pharmaceutical use of antisense oligonucleotides included "the inability to routinely deliver an effective concentration of a specific nucleic acid in a target cell such that a target gene is inhibited to a degree necessary to produce a therapeutic effect. The Examiner also argued that cell culture results "are generally not predictive of *in vivo* inhibition and the methods of delivery to a cultured cell would not be applicable to delivery of oligonucleotides to any organism."

First, Applicants note that, according to MPEP § 2164.02: "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." ... An applicant need not have actually reduced the invention to practice prior to filing. *In Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)." Further, Applicants note that, according to MPEP § 2164.02, "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)."

As the Examiner knows, many different antisense oligonucleotides have been found capable of reducing expression of a target gene *en vivo*. For example, Wahlestedt et al. (*Proceedings of the National Academy of Sciences USA* 97:5633-5638, 2000) conducted studies using a 15 residue oligonucleotide targeted to the rat δ-opiod receptor. The oligonucleotide consisted of 4 LNA residues followed by 6 DNA residues and then 5 LNA residues (DOR-AS-1 LNA/DNA/LNA gap-mer). The oligonucleotide was injected into the cerebrospinal fluid of rats. The treatment knocked down expression of DOR, a G-protein coupled receptor and altered the response of the mice to pain in the presence of an opiate. Thus, the DOR-AS-1 LNA/DNA/LNA gap-mer had a marked *en vivo* effect. Thus, oligonucleotides can reach targets *en vivo* and exert a physiological effect. Wahlestedt et al. conclude that the tested oligonucleotides containing DNA and LNA exhibited "(i) biological stability, (ii) RNase H activation, (iii) lack of toxicity, and (iv) potent biological activities." The Examiner has not provided any reasoning to doubt that the oligonucleotides of the present claims would not likewise be able effective *en vivo*.

The oligonucleotides of the present claims, unlike those described in the Wahlestedt et al., include at least one alpha-L-oxy LNA residue. However, this is not a reason to conclude that the oligonucleotides of the present claims would not likewise be effective *en vivo*. As explained in the present specification, oligonucleotides containing alpha-L-oxy LNA residues are effective antisense molecules in cells culture and in animals. In fact, as the present specification explains, oligonucleotides that include alpha-L-oxy LNA residues can have advantages.

The significance of use alpha-L-oxy LNA in antisense oligonucleotides can be best understood by first considering the role of LNA in antisense oligonucleotides. LNA induce very significant increases in thermal stability of duplexes toward complementary DNA and RNA. Thus, each LNA residue in an oligonucleotide can increase the melting temperature of a duplex of the oligonucleotide and complementary RNA by 3 to11°C compared to a DNA residue. This increased stability of oligonucleotide-mRNA duplexes is of obvious benefit in one of the two mechanisms by which antisense oligonucleotides are believed to knock down gene expression: steric hinderence of translational machinery. The increased stability conferred by LNA residues has led to widespread use of LNA containing antisense oligonucleotides, at least three of which are currently in clinical trials. However, it was found that LNA containing oligonucleotides hybridized to mRNA will not activate RNase H unless a continuous stretch of DNA residues is present in the oligonucleotide. This led to the design of so-called gapmer oligonucleotides in which a stretch of DNA residues are flanked by LNA residues. In such designs the LNA residues confer high-affinity hybridization to RNA while the stretch of DNA residues confers RNase H activity. In this way it is possible to design oligonucleotides that form stable oligonucleotide-mRNA duplexes that activate RNase H.

Alpha-L-oxy LNA residues, like beta-D-oxy-LNA, confer increases in thermal stability of duplexes toward complementary DNA and RNA. In addition, as explained in greater detail below: oligonucleotides containing alpha-L-oxy LNA exhibit efficient cellular uptake, oligonucleotides containing alpha-L-oxy LNA exhibit potent antisense activity in cell, and oligonucleotides containing alpha-L-oxy LNA residues can activate RNase H activity even in the absence of a stretch of DNA residues.

As explained at paragraph [0180] of the present specification, a 16 residue oligonucleotide having a central 9 DNA nucleotide portion flanked by alpha-L-oxy LNA residues exhibited higher unassisted cellular uptake (i.e., cellular uptake in the absence of a transfection agent) than an oligonucleotide containing only beta-D-oxy-LNA.

In addition, as explained at paragraphs [0181]- [0184] of the present specification, both fully and partially thiolated oligonucleotides containing alpha-L-oxy LNA residues exhibited assisted cellular uptake that is comparable to an oligonlucotide containing LNA (beta-D-oxy-LNA). Moreover, the subcellular localization of the alpha-L-oxy LNA residue containing oligonulceotides was found to be comparable to that of the LNA (beta-D-oxy-LNA) containing oligonucleotides.

As explained at paragraphs [0185] –[0190] of the present specification, alpha-L-oxy LNA residue containing oligonucleotides exhibit potent antisense activity against luciferase in a cell culture assay. In addition, as explained at paragraphs [0198] – [0200] of the specification, an alpha-L-oxy LNA can be placed within the DNA portion of so-called gapmer and the oligonucleotide will still elicit down-regulation. In contrast, a beta-D-oxy-LNA located in the gap results in a dramatic loss in down-regulation.

Given that oligonucleotides within the claims exhibit good cellular uptake and an elicit RNase H activity, and given that beta-D-oxy-LNA containing oligonucleotides have exhibited *en vivo* physiological effects, there is no reasonable basis for doubting that the presently claimed oligonucleotides will be pharmaceutically effective.

In view of the forgoing, Applicant respectfully requests that claim 70 not be rejected under 35 U.S.C. §112, first paragraph.

VI. Obviousness-type Double Patenting

Claims 43-47, 54,-60, 62 and 65-68 were provisionally rejected on the ground of obviousness-type double patenting as unpatentable over claims 43, 47-51, 53 and 55-96 of U.S. Application No. 10/717,434.

Applicant defers addressing this rejection until such time as the Examiner indicates that there are otherwise allowable in the present application.

VII. Conclusion

Applicant respectfully submits that the amendment and remarks made herein overcome the grounds of rejection and place the application in condition for allowance.

Please apply any required fees or any credits to deposit account number 06-1050, referencing Attorney Docket number 22460-003US1.

Respectfully submitted,

Date: 3 October 2008

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